the organocobalt complex. The bioactive agent is released from the bioconjugate by the cleavage of the covalent bond between the bioactive agent and the cobalt atom in the organocobalt complex, as described herein.

The bioactive agent is any agent which is desired to be delivered to cells, tissues or organs for nutrient or therapeutic effects. In accordance with the present invention, bioactive agents include, but are not limited to, nutrients, pharmaceuticals, drugs, peptides and oligonucleotides.

The organocobalt complex is any organic complex containing a cobalt atom having bound thereto 4-5 nitrogen and/or chalcogens such as oxygen, sulfur, etc., as part of a multiple unsaturated heterocyclic ring system. In accordance with the present invention, suitable organocobalt complexes include, but are not limited to, cobalamin, Co[SALEN], organo-(pyridine)bis(dimethylglyoximato)cobalt, corrinoids, derivatives thereof and analogues thereof. The organocobalt complexes may be unsubstituted or substituted with conventional organic functional groups which will not alter the basic nature of the organocobalt complex. The basic nature of the organocobalt complex is to directly or indirectly bind the bioactive agent covalently to the cobalt such that the cobalt-bioactive agent bond is readily cleavable as described herein. The organocobalt complex may also be covalently bound directly or indirectly to a targeting molecule. The targeting molecule is a molecule for which the desired cell, tissue or organ has a requirement or a receptor, as described herein.

The bioconjugate according to the present invention is administered to a subject in need of therapeutic treatment. The bioconjugate concentrates in a targeted cell, tissue or organ site as a result of the organocobalt complex. As an example, a bioconjugate containing a chemotherapeutic is administered to a patient and the bioconjugate concentrates in neoplastic cells where the active chemotherapeutic is released from the bioconjugate by cleavage. Similarly, other pharmaceuticals, drugs, peptides or oligonucleotides are administered to a subject as part of the bioconjugate which is concentrated in the desired cells, tissues or organs. The pharmaceuticals, drugs, peptides or oligonucleotides are released by cleavage. In one embodiment, the cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic aciton. In a second embodiment, the cleavage is caused to occur selectively at the release site by an external signal. The external signal may be light or photoexcitation, i.e. photolysis, or it may be ultrasound, i.e. sonolysis. Further, if the photolysis takes place in the

presence of a magnetic field surrounding the release site, the release of the drug, such as a cytotoxic agent, into surrounding healthy tissue can be minimized.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the structure and absorption spectrum of methylcobalamin (B_{12}).

Figure 2 shows the structure and absorption spectrum of ethyl-Co[SALEN] (cobalt-bis-[salicylidene]-ethylenediamine.

Figure 3A shows a sequential absorption spectra of aqueous CH_3-Cbl^{III} as a function of anaerobic sonolysis (pH 7.38, 100 mM Hepes, saturating Ar).

Figure 3B shows the change in absorbance spectra following aerobic sonolysis in the absence of organic buffer.

Figure 4A shows a sequential absorption spectra of aqueous compound **3** (Example 6) as a function of anaerobic sonolysis at pH 7.4, 100 mM Hepes, saturating Ar.

Figure 4B shows the change in absorbance spectra following aerobic sonolysis of a compound **3** (Example 6) solution containing phosphate buffer.

Figure 5 shows the effect of a chlorambucil bioconjugate on cell viability for the HCT-116 cell line. The results are shown for chlorambucil (■), the chlorambucil bioconjugate with photolysis (○), the chlorambucil bioconjugate with no photolysis (▲) and the chlorambucil bioconjugate plus 10 equivalents of hydroxycobalamin with photolysis (▽).

Figure 6 shows the effect of a chlorambucil bioconjugate on cell viability for the HL-60 cell line. The results are shown for chlorambucil (■), the chlorambucil bioconjugate with no photolysis (▲) and the chlorambucil bioconjugate plus 10 equivalents of hydroxycobalamin with no photolysis (▽).

Figure 7 shows the effect of a chlorambucil bioconjugate on cell viability for the B-16 cell line. The results are shown for chlorambucil (■), the chlorambucil bioconjugate with photolysis (○), the chlorambucil bioconjugate with no photolysis (▲) and the chlorambucil bioconjugate plus 10 equivalents of hydroxycobalamin with photolysis (▽).

Figure 8 shows the effect of a chlorambucil bioconjugate on cell viability for the Meth-A cell line. The results are shown for chlorambucil (■), the chlorambucil bioconjugate with photolysis (○), the chlorambucil bioconjugate with no photolysis (▲) and the chlorambucil bioconjugate plus 10 equivalents of hydroxycobalamin with photolysis (▽).

Figure 9 shows the effect of a chlorambucil bioconjugate on cell viability for the RD-995 cell line. The results are shown for chlorambucil (■), the chlorambucil bioconjugate with photolysis (○), the chlorambucil bioconjugate with no photolysis (▲) and the chlorambucil bioconjugate plus 10 equivalents of hydroxycobalamin with photolysis (▽).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to bioconjugates and the delivery of bioactive agents which are preferably targeted for site-specific release in cells, tissues or organs. More particularly, this invention relates to bioconjugates which comprise a bioactive agent and an organocobalt complex. The bioactive agent is covalently bonded directly or indirectly to the cobalt atom of the organocobalt complex. The bioactive agent is released from the bioconjugate by the cleavage of the covalent bond between the bioactive agent and the cobalt atom in the organocobalt complex. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site by application of an external signal. The external signal may be light or photoexcitation, i.e. photolysis, or it may be ultrasound, i.e. sonolysis. Further, if the photolysis takes place in the presence of a magnetic field surrounding the release site, the release of the bioactive agent into surrounding healthy tissue is minimized.

The bioconjugate according to the present invention is administered to a subject in need of therapeutic treatment. The bioconjugate concentrates in a targeted cell, tissue or organ site as a result of the organocobalt complex. The bioactive agent is released from the bioconjugate by cleavage. In one embodiment, the cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic aciton. In a second embodiment, the cleavage is caused to occur selectively at the release site by an external signal. The external signal may be light or photoexcitation, i.e. photolysis, or it may be ultrasound, i.e. sonolysis. Further, if the photolysis takes place in the presence of a magnetic field surrounding the release site, the release of the drug, such as a cytotoxic agent, into surrounding healthy tissue is minimized.

As one example, the bioconjugate contains a chemotherapeutic agent and is administered to a patient having cancer. In this example, a therapeutically effective amount of the bioconjugate is administered intravenously to a patient such that the bioconjugate concentrates in the neoplastic cells. The chemotherapeutic agent is released from the bioconjugate by natural